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Age at transplantation and outcome after autologous stem cell transplantation in elderly patients with multiple myeloma

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BACKGROUND AND OBJECTIVE: The optimal treatment of patients with multiple myeloma (MM) is not well defined, in part because these patients are underrepresented in clinical studies. Autologous stem cell transplantation (auto-SCT) after high-dose melphalan chemotherapy can result in a prolonged response duration and survival in patients under 65 years of age.

DESIGN AND SETTING: Single-center, retrospective study of patients treated at Paoli-Calmettes Institute Cancer Centre, between January 1994 and January 2007 (96 months)

PATIENTS AND METHODS: We compared the outcome of elderly (age >65 years) patients with younger patients aged between 60 and 65 years with MM.

RESULTS: We compared 82 elderly patients with 104 younger patients. Except for age, both groups had comparable demographic features, disease characteristics, and prognostic factors. Induction VAD chemotherapy was comparable between the elderly (87%) and younger (94%) group. Prior to auto-SCT, the calculated hematopoietic cell transplantation-specific co-morbidity index was also comparable. With a median follow-up of 41 months (range, 5-227 months) after auto-SCT, 120 patients were still alive. Disease progression (n=40; 61%) was the main cause of death, and it was comparable in the two groups. Auto-SCT-related mortality was 3.8% (n=4/104) in younger and 3.7% (n=3/82) in older patients. Comparing younger/older subjects, progression-free survival was significantly higher in the younger group (*P*<.0001). However, disease response rates after the first auto-SCT was comparable and overall survival (OS) was also comparable (57% vs. 54% at 5 years, *P*=NS; 32% vs. 24% at 10 years, *P*=NS). In a Cox multivariate analysis model, none of the relevant characteristics was shown to be a critical prognostic feature for OS.

CONCLUSIONS: Age was insignificant for both OS and transplant-related mortality. We conclude that there is no biological justification for an age-discriminate policy for MM therapy. Physiologic aging is likely more important than chronologic aging.

Multiple myeloma (MM) is a lymphoid disease of the elderly with a median age of onset of 65 years, and a median survival of three years. Currently, the optimal treatment for patients more than 65 years old is not well defined, in part because these patients are underrepresented in clinical studies, and this population is very heterogeneous in disease and demographic characteristics. Autologous stem cell transplantation (auto-SCT) after high-dose melphalan chemotherapy can result in a prolonged response duration and survival in patients under 65 years.[1,2]

Since the introduction of auto-SCT for MM, our patients were eligible for high-dose therapy up to age 70.[3-5] In recent years, we essentially discontinued an upper age limit when disease severity was judged to outweigh the anticipated toxicities from HDT, as per the recommendation of the French Francophone Myeloma Intergroup (IFM).

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Unfortunately, only a few patients with MM are able to receive HDT. However, this therapeutic approach is proposed more and more in older patients because of improvements in supportive care in the last years, particularly the use of the granulocyte-colony stimulating factor (G-CSF), which has reduced significantly the transplant-related mortality (TRM). Moreover many studies have shown the efficacy and tolerability of autotransplantation in some selected myeloma patients more than 65 years old.[1,6-8]

The realization of an autologous SCT in older patients presents several challenges in the field of the clinical research. The first of these challenges is related to the selection of patients to identify those clearly able to profit from this therapeutic strategy and especially those who can tolerate the intensive chemotherapy with minimal toxicity. Indeed, some factors related to each patient, like comorbidities or performance status, or factors related directly to the myeloma disease still need to be identified. The concept of patient stratification is very important to distinguish the concept "of physiological age" from that of "the chronological age". The second challenge is related to the best regimen of conditioning for auto-SCT and the use of the best intensive chemotherapy so as to maximize the efficacy and reduce the toxicities in these fragile old patients.

Recently, TRM has decreased considerably due to prompt neutrophil recovery with peripheral blood stem cell (PBSC) rescue so this treatment can be considered in individuals with myeloma over the age of 65 years.[5,9-12] These patients have previously been excluded from high-dose programs purely on the basis of age, but have otherwise met all the other prerequisites. Lastly, in elderly patients, prophylactic care after intensive chemotherapy is an important objective to preserve the quality of life of these patients. So the auto-SCT in older myeloma patients requires individual consideration taking into account of the heterogeneity and the relative comorbidities in this special population.

PATIENTS AND METHODS

This single center retrospective analysis assessed the outcome of consecutive MM patients aged over 60 years, treated with auto-SCT at the Institut Paoli-Calmettes Cancer Centre, Marseille, France, treated between January 1994 and January 2007 (96 months) with the specific aim to compare the outcome of "elderly" (age >65 years) patients, with "younger" patients aged between 60 and 65 years treated in the same period and in the same auto-SCT program.

The type of mobilization regimen for PBSC collection was similar in both groups, with G-CSF alone or

Table 1. Baseline characteristics and treatments received prior to auto-SCT.

Characteristic	Total population n=186 (%)	60-65 years group n=104 (%)	>65 years group n=82 (%)	P*
Median age (range; years)	64 (60-77)	61.9 (60-65)	68.5 (65.1-77)	NA
Male/Female	103 (55) / 83 (45)	61 (59) / 43 (41)	42 (51) / 40 (49)	.31
Myeloma stage at diagnosis[a]				
I	20 (11)	12 (12)	8 (10)	
II	24 (13)	16 (15)	8 (10)	.45
III	142 (76)	76 (73)	66 (80)	
Monoclonal component				
IgG	101 (55)	57 (55)	44 (54)	
IgA	47 (25)	27 (26)	20 (24)	
Light chain	36 (19)	19 (18)	17 (21)	.97
Non secretory	1 (0.5)	1 (1)	0	
IgD	1 (0.5)	0	1 (1)	
Light chain				
Kappa	121 (66)	72 (69)	49 (60)	
Lambda	55 (30)	29 (28)	26 (32)	.16
Other	10 (4)	3 (4)	7 (8)	
Cytogenetic at diagnosis				
Normal	164	92	72	
Del(13) Del (17) t (4;14)	22	12	10	.9
Beta-2 microglobulinemia				
≤ 2.5	120 (64)	67 (64)	53 (65)	
> 2.5	66 (36)	37 (36)	29 (35)	.98
Induction therapy at diagnosis				
VAD	169 (91)	98 (94)	71 (87)	
MP	3 (2)	1 (1)	2 (2)	.20
Other	14 (7)	5 (5)	9 (11)	
Comorbidity score prior to auto-SCT[b]				
0	125 (68)	70 (67)	55 (67)	
1	15 (8)	10 (10)	5 (6)	
2	15 (8)	6 (6)	9 (11)	.20
3	21 (11)	10 (10)	11 (13)	
>3	7 (4)	5 (4)	2 (2)	
Not available	3 (2)	3 (3)	0	

[a]According to Salmon and Durie classification; [b]The comorbidity score index was calculated using Sorror score.
VAD: vincristine, Adriamycin (doxorubicin), dexamethasone; MP: oral melphalan, prednisone.
Values are n (%) or n.

Table 2a. Auto-SCT features and transplant-related events.

Characteristic	Total population N=186 (%)	60-65 years group n=104 (%)	>65 years group n=82 (%)	P
Mobilization regimen PBSC collection				
G-CSF alone	113 (61)	57 (55)	56 (68)	
Chemotherapy and G-CSF	73 (39)	47 (45)	26 (32)	.20
Performance status at time of auto-SCT				
0	90 (48)	32 (31)	58 (71)	
1	81 (43)	60 (58)	21 (26)	
2	14 (8)	11 (10)	3 (4)	<.0001
3	1 (1)	1 (1)	0	
Disease status at time of auto-SCT				
CR or VGPR	24 (13)	15 (15)	9 (11)	
PR	119 (64)	64 (61)	55 (67)	
SD	12 (7)	3 (3)	9 (11)	.11
Refractory	21 (11)	13 (12)	8 (10)	
Not evaluable	10 (5)	9 (9)	1 (1)	
Auto-SCT conditioning regimen (mg/m²)				
Melphalan 100	15 (8)	0	15 (18)	
Melphalan 140	113 (61)	56 (54)	57 (70)	
Melphalan 200	53 (28)	45 (43)	8 (10)	<.0001
Other	5 (3)	3 (3)	2 (2)	
Time (days) to ANC>500/µL (median, range)[a]	13 (6-25)	13 (6-25)	14 (8-22)	.25
Time (days) to platelets>20000/µL (median, range)[b]	15 (8-32)	14.5 (8-32)	15 (9-26)	.049
Total length (days) of hospitalization during auto-SCT (median; range)	18 (2-39)	19 (2-32)	17 (2-39)	.18
Mucositis[c]				
Grade 0-1	40 (29)	14 (20)	26 (42)	
Grade 2	53 (38)	28 (40)	25 (37)	.039
Grade 3-4	45 (33)	28 (40)	17 (25)	

[a]Data available for 169 patients; [b]Data available for 140 patients; [c]Data available for 138 patients.
Abbreviations: ANC: absolute neutrophil count; auto-SCT, one or more autologous stem cell transplantations; CR, complete remission; PR, partial remission; VGPR, very good partial response; PD, progressive disease; SD, stable disease.

with chemotherapy; the performance status at time of auto SCT, and the disease status at the time of auto SCT was similar also. Before being admitted for high-dose melphalan and autologous SCT, all patients were screened for the absence of cardiac failure (checkup included echocardiography with a required a forced expiratory volume > 50%, or an absence of respiratory failure; diffusing capacity for carbon monoxide > 50%), and renal or hepatic failure (biological parameters). Patient characteristics were matched for the main risk factors previously identified to affect event-free survival and overall survival (OS) after autotransplants.[10,11] Hematopoietic cell transplantation-specific co-morbidity index (adapted from the Charlson Comorbidity Index" was calculated for each patient.

All data were computed using SPSS for Windows (SPSS Inc., Chicago, IL) and SEM software (SILEX, Mirefleurs, France). The Mann–Whitney test was used for comparison of continuous variables. Categorical variables were compared using the chi-square test, the cumulative incidence method as previously described. Cumulative incidence estimates were also used to measure the probability of relapse or progression.[13] OS was calculated from the date of the first auto SCT to death from any cause. Progression-free survival (PFS) was calculated from the date of the first auto-SCT to disease progression, disease relapse, or patient death. PFS and OS were estimated from the time of the first auto-SCT using the Kaplan-Meier product-limit estimates. Differences between groups were tested using the log-rank test.[14]

RESULTS

This single-center retrospective analysis evaluated the results of 186 consecutive patients with MM treated by auto-SCT over a period of 96 months. We compared the results of 82 "old patients" (age> 65 years) who were matched with 104 "young patients" (age between 60 and 65 years) treated during the same time and with the same program of auto-SCT. The median age in our total population of 186 patients was 64 years (range, 60-77 years). The median age in the younger group was 61.9 years and in the older group was 68.5 years (**Table 1**). Except for age, the two groups were comparable (differences statistically nonsignificant) in demographic and disease (the stage of the disease, monoclonal components) characteristics and in prognostic factors (bêta2-microglobulin). The distribution of sex in the two groups was not significantly different. There was no difference between the groups in the myeloma stage at diagnosis, the type of monoclonal component protein, the light chain type, the rate of beta-2 microglob-

ulinemia, the type of induction therapy at diagnosis, the comorbidity score prior auto-SCT. Specifically, the incidence of favorable cytogenetics (absence of aberrations of chromosomes 13 and 17 as well as any translocation) was similar in the young patients and the older cohorts (**Table 1**).

The majority of the patients (91%) received VAD homogeneous induction chemotherapy, which was comparable between the old patients (87%) and the young patients (94%). There were some statistically significant differences in melphalan dose as a conditioning regimen; 45 (43%) patients received melphalan at a full dose at 200mg/m^2 in the young group compared to only 8 (10%) patients in the older group; (*P*<.0001). Before the realization of the auto-SCT, the evaluation of the comorbidities with the score of Charlson adapted to the SCT was also comparable between the two groups (77% of the young patients presenting a score 0-1, against 73% in the group of the old patients; *P*=NS).

There were some differences between the two groups in performance status at time of auto-SCT that were statistically significant; 12 (11%) patients in the young group vs 3 (4%) patients in the older group had a PS grade 2-3; (*P*<.0001) (**Table 2a**). Thirty-three percent of the young patients and 28% of the old patients (*P*=NS) received a second auto-SCT.

The most common adverse reactions to stem cell infusion were nausea and vomiting; hypertension or tachycardia and they were not different between the two groups. There was no difference in longer post-transplant hospital stay for the elderly group in median (17 days) or range (2-39) compared with the younger group (19 days) or range (2-32); (*P*=0.18) The proportion of patients attaining WBC engraftment (as indicated by an absolute neutrophil count (ANC) >500 for three consecutive days) was similar in both groups, (*P*=0.25) (**Table 2a**). Similarly, the proportion of patients achieving a platelet count over 20 000 was similar for both groups. The most common post-transplant toxicities that were encountered included nausea, mucositis, diarrhea and neutropenic fever. Post-transplant mucositis was not different in the two groups, but important mucositis (grade 3-4) was statistically significantly greater in the younger group (*P*=.039) probably because of the lower doses of melphalan received in the older group. The incidence of post-transplant bacteremias, fungal and interstitial pneumonia was similar in the two groups (**Table 2b**). There was no difference also in other serious life-threatening complications, the number of patients transferred in the ICU, or in the number who

Table 2b. Auto-SCT features and transplant-related events.

Characteristics	Total population N=186 (%)	60-65 years group n=104 (%)	>65 years group n=82 (%)	P
Documented infections[a]				
Bacteria	34 (18)	18 (17)	16 (20)	
Fungal	8 (4)	7 (7)	1 (1)	.10
Interstitial pneumonia	10 (6)	8 (8)	2 (3)	
None	134 (72)	71 (68)	63 (77)	
Other serious or life-threatening complications	19 (10)	12 (12)	7 (9)	.50
Patients transferred to the ICU	12 (7)	6 (6)	6 (7)	.67
Response after the first auto-SCT				
CR or VGPR	84 (45)	50 (48)	34 (41)	
PR	82 (44)	42 (40)	40 (49)	
SD	1 (1)	1 (1)	0	.58
Progressive	12 (6)	8 (8)	4 (5)	
Not evaluable	7 (4)	3 (3)	4 (5)	
Cause of death (total no.)	66 (35)	40 (38)	26 (32)	
Disease	40 (61)	27 (26)	13 (2)	
Transplant-related mortality	7 (11)	4 (4)	3 (4)	.44
Infections	10 (15)	4 (4)	6 (7)	
Other	9 (14)	5 (5)	4 (5)	
Disease status at last follow-up				
CR or VGPR	37 (20)	19 (18)	18 (22)	
PR	17 (9)	9 (9)	8 (10)	
SD	36 (19)	22 (21)	14 (17)	.86
Progressive	92 (50)	51 (49)	41 (50)	
Not evaluable	4 (2)	3 (3)	1 (1)	

[a]Non-microbiologically documented infections were not analyzed.
Abbreviations: auto-SCT, one or more autologous stem cell transplantations; CR, complete remission; PR, partial remission; VGPR, very good partial response; PD, progressive disease; SD, stable disease.

died of transplant-related causes.

One hundred twenty patients were still alive after autoSCT, with a median follow-up of 41 months (range, 5-227 months). Disease progression (n=40; 61%) was the main cause of the death, at a comparable rate in the two groups (**Table 2b**). PFS after the first auto SCT was significantly higher in the young
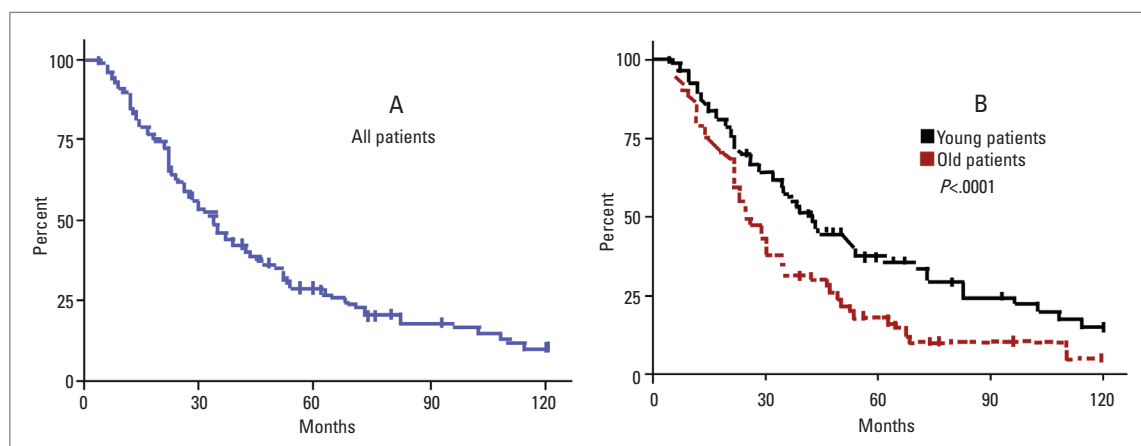
Figure 1. Progression-free survival for all patients (A) and for young (age 60-65 years, n=104) and older patients (age >65 years, n=82).
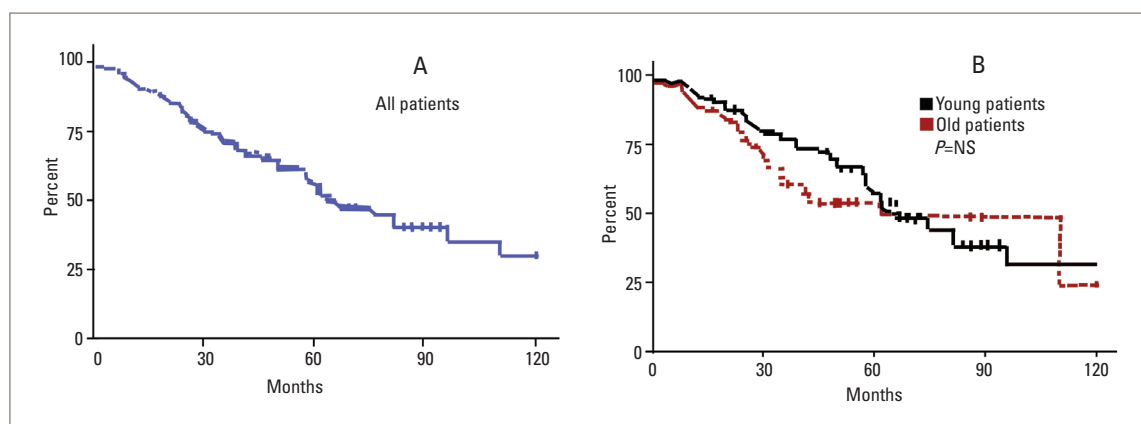

Figure 2. Overall survival for all patients (A) and for young (age 60-65 years, n=104) and older patients (age >65 years, n=82).

patients (37% vs 22% at 5 years) (*P*<.0001) (Figure 1). The median PFS was 45 months in the younger patients vs 27 months in the older patients, probably because the older patients had more frequently received melphalan 140 mg/m² instead 200mg/m². However, the remission rate after the first auto-SCT was comparable (the rate of CR, VGPR and PR: 88% against 90%, *P*=NS) and the overall survival (OS) were also comparable (57% vs 54% at 5 years, *P*=NS and 32% vs 24% at 10 years, *P*=NS) (Figure 2).

The TRM as cause of death was compared in the two groups (**Table 2b**). Disease status at the last follow up was also comparable: CR or VGPR+PR and disease progression at the last follow up was comparable. In a multivariate analysis, none of the analyzed characteristics (age, melphalon dose, disease status of the transplant) had a significant impact on the overall survival. Also we did not find an influence of age on survival nor on TRM.

DISCUSSION

We have demonstrated a similar outcome for patients older than 65 years and for patients in the 60-65 year old population. This matched analysis allows for a better estimate of the outcome of these patients, by eliminating the effect of different prognostic factors that could often be biased in single group retrospective studies.[15,16] We did not observe any significant differences in the response rates or in the time-to-progression following transplant between the two groups. We also observed that high-dose melphalan with auto-SCT is feasible and effective in old patients with MM. The results obtained plead in favor of an equivalent benefit in terms of survival in old patients more than 65 years of age, without an increased risk of toxicity or mortality.[17,18]

In our analysis, the evaluation of comorbidities with the score of Charlson adapted to transplanted patients showed that the group of young patients is comparable with the group old patients.[19-21] This is important data,

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which pleads in favor of a precise selection of these patients because it is allowed because it is commonly believed that older patients have more comorbidities.[22,23] However, the evaluation of comorbidities cannot reflect perfectly or adequately these characteristics in connection with "the physiological reserves" in older patients. Indeed, the personal clinical and functional onco-geriatric status of patients can be very variable in spite of similar age and comparable comorbidities.[24] Beyond the development of method for a better selection of the patients, it appears important, in the context of intensive chemotherapies with auto-SCT in older myeloma patients, to consider the development of a chemotherapy approach specifically adapted to age.[25-27]

Indeed, the ideal posology for melphalan as the best conditioning regimen to auto-SCT was largely defined in some studies, but with sometimes contradictory results.[1,15,16] Moreover, it is important to note that within the framework of our study, the oldest patients more frequently received melphalan at 140 mg/m² instead of 200 mg/m², which supported certainly the reduction of various toxicities. Also in the elderly group, 15 patients (18 %) received 100 mg/m² and 8 of those patients underwent a second auto-SCT as part of planned tandem transplant (Table 2a).

In addition, the availability of new anti-myeloma agents much more specific and less toxic properties (lenalidomide and bortezomib), should allow for the development of more modern approaches for conditioning and less toxicity, including for example, a less important role (a lower dose) of melphalan in combination with one or more of these drugs.[28]

The natural history of multiple myeloma is in a phase of important change. Major therapeutic progress in the last 5 years has made it possible to transform this pathology almost into a chronic disease that evolves over several years with patients receiving a multitude of therapeutic lines with alternation of phases of relapse and remission. The availability of these more targeted and probably less toxic approaches than auto-SCT should however hide the potential benefit of autotransplantation in these patients. New approaches are necessary to evaluate the place of auto-SCT in combination with other modern treatments in all patients with MM, including the oldest patients.

Thalidomide, bortezomib, and lenalidomide have been combined with corticosteroids, alkylators, and anthracyclines in front-line MM treatment.

Until recently, high rates of CR and other major responses were primarily seen with autologous SCT in young patients, but insights into the biology of MM have led to the development and approval of new drugs with significant activity, and new induction regimens based on these novel agents are offering improved responses. The substantial activity seen with these new drug combinations has prompted a re-examination of the role of autologous SCT in MM treatment. Will achievement of major responses with these new regimens translate into improved survival after consolidation with transplantation? Will these improved induction regimens reduce the need for tandem transplantation, or does achievement of CR obviate the need for front-line transplantation altogether? Is there still a role for autologous SCT in elderly MM patients in the era of novel drug? To help address these questions, randomized trials are needed, as well as tests with improved sensitivity to better define depth of remission. [26] Beyond the objectives of survival and toxicity, it appears increasingly important to incorporate in clinical research protocols the secondary objectives as the measurement of the quality of life or the functional status of the patient which should bring additional arguments in favor of one or the other of the therapeutic sequences.

This report confirms our previous experience that age per se does not affect outcome after autotransplant for MM, whether examined as a continuous or categorical variable. This finding may be due, in large part, to the availability of adequate quantities of CD34+ cells in young and old patients, assuring comparable durations of neutropenia and thrombocytopenia and, thus, minimizing the risk of infection and other toxicities. Accumulative injury from a second HDT cycle to either the bone marrow micro-environment or other critical organs was not apparent in either age group. On the basis of our data we conclude that optimal therapy for MM with PBSC-supported high-dose melphalan therapy should not be withheld from the majority of older patients presenting with MM who deserves optimal control of their disease and, thereby, gaining hopefully many years of high-quality life.

Author contributions
Jean El-Cheikh: collected and analyzed data, performed statistical analysis, wrote and revised the manuscript. Elias kfoury: collected data provided clinical care and reviewed the manuscript. Anne-Marie Stoppa, Diane Coso, Reda Bouabdallah, Jean-Albert Gastaut: recruited patients provided clinical care and reviewed the manu-

REFERENCES

1. Badros A, Barlogie B, Siegel E, Morris C, Desikan R, Zangari M et al. Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. Br J Haematol 2001; 114: 600-607.

2. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78: 21-33.

3. Blade J, Munoz M, Fontanillas M, San Miguel J, Alcala A, Maldonado J, et al. Treatment of multiple myeloma in elderly people: long-term results in 178 patients. Age Ageing 1996; 25: 357-361.

4. Rodon P, Linassier C, Gauvain JB, Benboubker L, Goupille P, Maigre M, et al. Multiple myeloma in elderly patients: presenting features and outcome. Eur J Haematol 2001; 66: 11-17.

5. Clavio M, Casciaro S, Gatti AM, Spriano M, Bonanni F, Poggi A, et al. Multiple myeloma in the elderly: clinical features and response to treatment in 113 patients. Haematologica 1996; 81: 238-244.

6. O'Shea D, Giles C, Terpos E, Perz J, Politou M, Sana V, et al. Predictive factors for survival in myeloma patients who undergo autologous stem cell transplantation: a single-centre experience in 211 patients. Bone Marrow Transplant 2006; 37: 731-737.

7. Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, Nunzi M, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood 2004; 104: 3052-3057.

8. Siegel DS, Desikan KR, Mehta J, Singhal S, Fassas A, Munshi N, et al. Age is not a prognostic variable with autotransplants for multiple myeloma. Blood 1999; 93: 51-54.

9. Desikan KR, Tricot G, Munshi NC, Anaissie E, Spoon D, Fassas A, et al. Preceding chemotherapy, tumor load and age influence engraftment in multiple myeloma patients mobilized with granulocyte colony-stimulating factor alone. Br J Haemato 2001; 112: 242-247.

10. Fietz T, Rieger K, Dimeo F, Blau IW, Thiel E, Knauf WU. Stem cell mobilization in multiple myeloma patients: do we need an age-adjusted regimen for the elderly? J Clin Apher 2004; 19: 202-207.

11. Guba SC, Vesole DH, Jagannath S, Bracy D, Barlogie B, Tricot G. Peripheral stem cell mobilization and engraftment in patients over age 60. Bone Marrow Transplant 1997; 20: 1-3.

12. Dumontet C, Ketterer N, Espinouse D, Neidhardt EM, Moullet I, Thieblemont C et al. Reduced progression-free survival in elderly patients receiving intensification with autologous peripheral blood stem cell reinfusion for multiple myeloma. Bone Marrow Transplant 1998; 21: 1037-1041.

13. Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999 Mar 30;18 (6):695-706.

14. Kaplan, E.L. & Meier, P. (1958) Non-parametric estimation from incomplete observations. Journal of the American Statistical Association, 53, 457±481.

15. Cohen HJ, Bartolucci A. Age and the treatment of multiple myeloma. South eastern Cancer Study Group experience. Am J Med 1985; 79: 316-324.

16. Palva IP, Ahrenberg P, Ala-Harja K, Almqvist A, Hanninen A, Ilvonen M et al. Treatment of multiple myeloma in old patients. Finnish Leukaemia Group. Eur J Haematol 1989; 43: 328-331.

17. Sirohi B, Powles R, Treleaven J, Mainwaring P, Kulkarni S, Pandha H, et al. The role of autologous transplantation in patients with multiple myeloma aged 65 years and over. Bone Marrow Transplant 2000; 25: 533-539.

18. Reece DE, Bredeson C, Perez WS, Jagannath S, Zhang MJ, Ballen KK, et al. Autologous stem cell transplantation in multiple myeloma patients < 60 vs > / = 60 years of age. Bone Marrow Transplant 2003; 32: 1135-1143.

19. Jantunen E, Kuittinen T, Penttila K, Lehtonen P, Mahlamaki E, Nousiainen T. High-dose melphalan (200 mg/m²) supported by autologous stem cell transplantation is safe and effective in elderly (> or = 65 years) myeloma patients: comparison with younger patients treated on the same protocol. Bone Marrow Transplant 2006; 37: 917-922.

20. Extermann M. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 2000; 35: 181-200.

21. Yancik R, Havlik RJ, Wesley MN, Ries L, Long S, Rossi WK, et al. Cancer and comorbidity in older patients: a descriptive profile. Ann Epidemiol 1996; 6: 399-412.

22. Lenhoff S, Hjorth M, Westin J, Brinch L, Backstrom K, Carlson K, et al. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. Br J Haematol 2006; 133: 389-396.

23. Terpos E, Apperley JF, Samson D, Giles C, Crawley C, Kanfer E, et al. Autologous stem cell transplantation in multiple myeloma: improved survival in nonsecretory multiple myeloma but lack of influence of age, status at transplant, previous treatment and conditioning regimen. A single-centre experience in 127 patients. Bone Marrow Transplant 2003; 31: 163-170.

24. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 1998; 279: 1187-1193.

25. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998; 16: 1582-1587.

26. Repetto L, Fratino L, Audisio RA. Venturino A, Gianni W, Vercelli M et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 2002; 20: 494-502.

27. Cesari M, Kritchevsky SB, Penninx BW, Nicklas BJ, Simonsick EM, Newman AB et al. Prognostic value of usual gait speed in well-functioning older people - results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005; 53: 1675-1680.

28. Bensinger WI. Stem-cell transplantation for multiple myeloma in the era of novel drugs. J Clin Oncol. 2008 Jan 20; 26(3):480-92. Epub 2007 Dec 3.